PATENT
Attorney Docket No. **CUTLER-06326**

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Neal R. Cutler
Serial No.: 09/899,412 Group No.: 1615
Filed: 07/05/01 Examiner: Joynes, R.
Entitled: **Sublingual Administration of Dihydroergotamine For The Treatment Of Migraine**

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF DELIVERY, VIA HAND DELIVERY UNDER 37 C.F.R. § 1.6(c)

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Dated: 8-8-03 By: Q. N. Molina

Sir or Madam:

Enclosed please find an Information Disclosure Statement, Form PTO-1449 including copies of the references contained thereon and a Preliminary Amendment, for filing in the U.S. Patent and Trademark Office.

The Commissioner is hereby authorized to charge any fee or credit overpayment to our Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: August 7, 2003

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#11
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Dated: 8-8-03 By: G. M. Molina

Sir:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are referred to in the body of the specification:

- U.S. Pat. No. 4,650,810 to Bays *et al.*;
- U.S. Pat. No. 4,914,125 to Baldinger *et al.*;
- U.S. Pat. No. 4,916,125 to Herrling *et al.*;
- U.S. Pat. No. 4,994,483 to Oxford *et al.*;
- U.S. Pat. No. 5,021,428 to Carr *et al.*;
- U.S. Pat. No. 5,200,413 to King *et al.*;
- U.S. Pat. No. 5,242,949 Goldberg *et al.*;

- U.S. Pat. No. 5,248,684 to Suzuki *et al.*;
- U.S. Pat. No. 5,273,759 to Simmons;
- U.S. Pat. No. 5,317,103 to Baker *et al.*;
- U.S. Pat. No. 5,364,863 to Cohen *et al.*;
- U.S. Pat. No. 5,399,574 to Robertson *et al.*;
- U.S. Pat. No. 5,434,154 to Smith *et al.*;
- U.S. Pat. No. 5,441,969 to Axelsson *et al.*;
- U.S. Pat. No. 5,464,864 to King *et al.*;
- U.S. Pat. No. 5,466,699 to Robertson *et al.*;
- U.S. Pat. No. 5,468,768 to Cipollina *et al.*;
- U.S. Pat. No. 5,491,148 to Berger *et al.*;
- U.S. Pat. No. 5,494,910 to North *et al.*;
- U.S. Pat. No. 6,200,604 to Pather;
- U.S. Pat. No. 6,221,392 to Khankari *et al.*;
- "Remington's Pharmaceutical Sciences", 17th ed., Mack Publishing Company (1985), p. 946[1]; and
- Goodman and Gilman's "The Pharmaceutical Basis of Therapeutics", 8th ed., McGraw-Hill, Inc. (1990), pp. 944-947.

Applicant has become aware of the following printed publications which may be material to the examination of this application:

- Becker *Can J Clin Pharmacol* 6 (Suppl A):15A-19A (1999) describes the use of antiemetic drugs in the treatment of migraine-associated nausea. It is noted that severe nausea and vomiting may interfere with the use of oral medications. Therefore alternative drug delivery methods are suggested, including sublingual administration (by tablet and oral wafers) and a nasal spray. This publication teaches treating patients with migraine associated nausea with dihydroergotamine (DHE) as a nasal spray and through subcutaneous injection.

[1] We have been unable to locate this reference, if the examiner requests a copy we will try to obtain it.

However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,891,885 to Caruso describes methods for treating migraine. These methods involve co-administering (or administering in combination) an antimigraine drug (which can be an ergot alkaloid, such as dihydroergotamine) and an anti-migraine potentiating amount of an NMDA receptor antagonist or agent which blocks a major intracellular consequence of NMDA receptor activation. Therapeutic compositions comprising antimigraine drug and an active ingredient that blocks NMDA receptor activation are contemplated. Numerous modes of administrating these compositions are contemplated, including topical administration in the mouth. Oral topical pharmaceutical compositions are provided in the form of buccal or sublingual tablets, drops or lozenges (see column 6, lines 22-25). This publication is silent on teaching the administration of an antimigraine drug *alone* without co-administering an NMDA receptor agonist (i.e. a second active ingredient). Therefore, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 6,197,331 to Lerner *et al.* describes an oral patch for controlled or sustained release of pharmaceutical agents in the oral cavity. The oral composition comprises an adhesive component and nonadhesive component, wherein said nonadhesive component includes ingredient(s) such as antimigraine agents, *e.g.* dihydroergotamine, and conditions to be treated included migraine. The patch adheres to hard dental surfaces (such as teeth and dentures), and release of the pharmaceutical agent is facilitated, which results in rapid systemic delivery of the released agent. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,942,251 to Merkus describes nasal formulations and nasal administration of certain pharmacologically active ingredients for the treatment of migraine. At least one formulation comprises dihydroergotamine, in combination with a cyclodextrin and/or other saccharides and/or sugar alcohols, and this is noted to be alternatives for oral, intravenous or intramuscular administration. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 6,010,719 to Remon *et al.* describes freeze-dried disintegrating tablets comprising a therapeutic agent, a matrix-forming agent (present in greater than 20% by weight) and a binding agent (preferably a thickening agent). The tablets preferably have a disintegration time of between 10 and 120 seconds as measured *in vitro* by subjects given tablets to place under the tongue (col 6, lines 53-55) and includes fast dissolving dosage forms for sublingual, buccal and oral administration. In Example 5 there is a suggestion of sublingual administration for "off" phases in Parkinsonian patients with motor fluctuations (see col 9, lines 15-21) however the therapeutic composition described does not include dihydroergotamine (col 8, line 66 - col 9, lines 1-10). Dihyroergotamine is disclosed in a laundry list of suggested therapeutic agents (col 12, lines 8-68). However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 6,139,819 to Unger *et al.* describes compositions which may be used diagnostically as contrast agents in imaging (*e.g.* ultrasound) or therapeutically for various diseases. The compositions comprise a lipid, a protein, a polymer and/or surfactant and a gas, in combination with a targeting ligand. As an example of a vesicle containing a bioactive agent, the patent teaches that dihydroergotamine can be used with heparin sulfate to decrease venostasis (col 60, lines 2-10). While injection is the preferred mode of administration, the compositions may be administered by other parental modes, including sublingual and buccal (see col 75 line 23). However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more

inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,672,356 to Rault *et al.* describes a bioadhesive composition for transmucosal drug delivery. In general, the composition comprises an active principle, a copolymer, acetylated maize starch, and therapeutically acceptable excipients, said composition being wet granulated and compressed into a tablet. The active principle includes antimigraines, of which no specific examples are listed (see col. 3, line 39) and includes excipients, *e.g.* calcium dihydrogenphosphate, magnesium stearate, disintegrants, etc. (col. 2, lines 3-5). This publication teaches controlled release of active principles including locally across the buccal cavity or systemically across a buccal (cheek or gum), perlingual, and for example in the maxillogingival groove of the buccal cavity or under the tongue (see col. 3, lines 17-18). Of note is Example 8 directed to a compression tablet of compressed powder comprising dihydroergotamine mesylate, microcrystalline cellulose, lactose, microcrystalline cellulose, Gantrez MS, magnesium stearate and colloidal silica. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,288,498 to Stanley *et al.* describes compositions of oral nondissolvable matrices for the transmucosal delivery of medicaments. These compositions comprise a drug containment matrix; a pharmacologically effective dose of a drug being capable of absorption through mucosal tissues of the mouth, pharynx, and esophagus, the pharmacologically effective dose of the drug being contained by the nondissolvable drug containment matrix; and holder means secured to the drug nondissolvable containment matrix. The drug containment matrix may take the form of, for example, a sponge or a barrier of a membrane or screen-like material which contains the drug. This publication teaches the use of pH buffering/adjusting agents to improve delivery. Among the drugs contemplated within the composition are antimigraines, including the antimigraine drug ergotamine (Table 3, col. 22) while dihydroergotamine is claimed as a specific drug (claim 80). However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a *fast dissolve* formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 4,963,367 to Ecanow describes drug delivery compositions and methods, wherein the drug delivery is accomplished by encapsulation of the drug by a coacervate derived film. Administration may be oral, or transmucosal (*i.e.* direct application to any of the accessible mucosal membraneous tissues of the body) among other means. Among the numerous drugs listed as being suitable for incorporation into the compositions is dihydroergotamine mesylate. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive

ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,051,426 to Parnell describes the use of a serotonin receptor antagonist in combination with a central nervous system stimulant for the treatment of a drug addicted individual (so that they can discontinue use of the drug without withdrawal symptoms). The preferred serotonin antagonist is dihydroergotamine (and dihydroergotamine mesylate). The compounds can be administered separately or simultaneously. Administration can be transmucosal, and nasal, oral and buccal. The compositions may contain magnesium carbonate. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,877,183 to Cincotta describes the administration of a D_1 or D_2 agonist (or both) and the administration of a $5HT_{1B}$ agonist, for the reduction in food consumption, body weight, serum glucose levels and/or serum triglyceride levels. Dihydroergotamine is described as a suitable D_2 agonist. Administration may be sublingual. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive

ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- Kiechel, "The Bioavailability and Kinetics of Dihydroergotamine" in Fitacha (Ed.); Neuester Scand Der Dihydergot Forschung. Sturtgart Georg Thiema: 32-46 (1984) describes various pharmacokinetic properties of dihydroergotamine (DHE). Various dosage forms and drug availability with are described, including oral drop solutions, tablets, capsules, micellar solutions, rectal suppositories, subcutaneous and intramuscular injection, intravenous injection and nasal administration. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,637,611 to King *et al.* describes compounds (tetrahydrocarbazoles) and their utility in treatment of disorders characterized by excessive vasodilatation (including migraines). The compounds may be administered sublingually. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,855,907 to Peyman describes methods for the treatment of migraine through the topical administration of a migraine-ameliorating amount of an opioid, either singly or in combination with (simultaneously or sequentially) other pharmacological agents, including vasoconstrictors, antiinflammatory agents, antimicrobial agents, decongestants, non-opioid migraine drugs (such as sumatriptan, valproate *etc.*) or steroids (such as glucocorticoid). Dihydroergotamine is noted to be used in the treatment of migraine administered intramuscularly or as a nasal spray. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 6,103,218 to Brucker *et al.* describes compositions and their use as a therapeutic nasal spray. Specifically, the compositions comprise feverfew, and may also contain nanoclustered water, vitamins, surfactants, wetting agents, emulsifiers, preservatives and odorants. The nasal spray is useful for moisturizing the nasal mucous membranes, relief of migraines and relief of spasmodic conditions (including menstrual cramps). However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,006,342 to Cleary *et al.* describes a transdermal drug delivery device. In one embodiment, transmucosal delivery is contemplated. Dihydroergotamine is among one of the drugs which can be used with the device. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,487,898 to Lu *et al.* describes formulations for sublingual administration of therapeutic agents, in particular, a peptide and pseudopeptide agents of 20 residues or less. The compositions comprise a solvent (an alcohol), optionally a cosolvent or hydrogel, and an oral mucosal transport enhancing agent (such as an essential or volatile oil and organic or inorganic acids). However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,955,502 to Hansen *et al.* describes the use of fatty acid esters as bioadhesive/mucoadhesive substances. An active agent (drug) can be administered to skin or mucosa by combining it with a bioadhesive fatty acid ester. Dihydroergotamine is among the drugs listed. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a

fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- Migranal (dihydroergotamine mesylate, USP) Nasal Spray Information, Novartis Pharmaceuticals Company, Inc. Publication 30721901, 1997 provides a description of a dihydroergotamine mesylate spray, including its mechanism of action, pharmacokinetics, adverse reactions and contraindications to its use as an acute treatment for migraine. Injectable solutions of dihydroergotamine mesylate are also mentioned. It is noted that dihydroergotamine mesylate is poorly bioavailable following oral administration. Moreover, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- D.H.E. 45 (dihydroergotamine mesylate) Injection, USP Information, Novartis Pharmaceuticals Company, Inc., Publication 30220906, 1998 provides a description of a dihydroergotamine mesylate injectable solution (for intravenous, intramuscular or subcutaneous use), including its mechanism of action, pharmacokinetics, adverse reactions and contraindications to its use as an acute treatment for migraine. Nasal sprays of dihydroergotamine mesylate are mentioned, and it is noted that dihydroergotamine mesylate is poorly

bioavailable following oral administration. Moreover, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 6,077,539 to Plachetka *et al.* describes a non-vasoactive composition to be used in the treatment of migraine. Specifically, rapidly available metoclopramide and at least one long-acting NSAID are administered (in a combined dosage form or coordinately) without 5HT agonist vasoactive agents (such as dihydroergotamine). The dosage form may be administered orally, sublingually and intranasally, among other methods. Some tablets contain effervescent agents. Ergots (including dihydroergotamine) are mentioned as being recognized treatments for migraine, and act most rapidly when given by the parenteral route. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 4,389,393 to Schor *et al.* describes a carrier base material combined with a therapeutically active medicament and shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon

administration. This reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 4,916,125 to Herrling *et al.* the treatment of migraine with the administration of a compound comprising pentenoic acid derivatives. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 4,933,367 to Wolff *et al.* teaches carboxylic acid derivatives and their use in the treatment of various diseases such as diabetes, prediabetic conditions, adipositas ailments or atherosclerosis. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation consisting of one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) a fast dissolve formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

- U.S. Patent 5,939,425 to Caruso *et al.* teaches methods of alleviating a migraine comprising the coadministration of: i) a migraine-treating amount of an antimigraine drug and 2) an antimigraine-potentiating amount of at least one member of the group consisting of nontoxic antagonist for the NMDA receptor and nontoxic substance that blocks a major intracellular consequence of NMDA receptor activation. However, this reference is silent on the sublingual administration, for the treatment of migraine, of: i) a fast dissolve formulation *consisting of* one active ingredient and one or more inactive ingredients, wherein said active ingredient is dihydroergotamine and one of said inactive ingredients is a pH adjusting agent or ii) *a fast dissolve* formulation consisting of first and second active ingredients and one or more inactive ingredients, wherein said first active ingredient is dihydroergotamine and said second active ingredient is selected from the group consisting of analgesics and anesthetics.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

Respectfully submitted,

Dated: August 7, 2003

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